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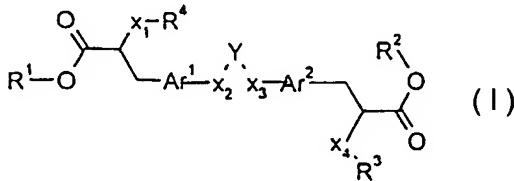
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(54) Title: NEW COMPOUNDS, THEIR PREPARATION AND USE

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(57) Abstract: The present invention relates to compounds of the general formula (I). The compounds are useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), wherein R¹, R², R³ and R⁴ independently of each other are hydrogen, C₁₋₁₂-alkyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or C₁₋₆-alkoxyC₁₋₆-alkyl, optionally substituted with one or more

halogen, hydroxy or amino; and X_1 , X_2 , X_3 and X_4 independently of each other is carbon, oxygen, sulphur or nitrogen; and Y is C_{1-12} -alkyl, C_{2-12} -alkenyl, C_{2-12} -alkynyl, aryl, aralkyl, alkylaralkyl, heteroaryl, heteroaralkyl, or alkylheteroaralkyl, optionally substituted with one or more halogen, hydroxy or amino; and Ar^1 and Ar^2 independently of each other are aryl or heteroaryl optionally substituted with one or more halogen, hydroxy, amino, aminoalkyl, carboxyalkyl, C_{1-6} -alkyl or C_{1-6} -alkoxy; or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

New Compounds, their Preparation and UseFIELD OF INVENTION

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The present invention relates to novel compounds, pharmaceutical compositions containing them, methods for preparing the compounds and their use as medicaments. More specifically, compounds of the invention can be utilised in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

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BACKGROUND OF THE INVENTION

Coronary artery disease (CAD) is the major cause of death in Type 2 diabetic and metabolic syndrome patients (i.e. patients that fall within the 'deadly quartet' category of impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

15

The hypolipidaemic fibrates and antidiabetic thiazolidinediones separately display moderately effective triglyceride-lowering activities although they are neither potent nor efficacious enough to be a single therapy of choice for the dyslipidaemia often observed in Type 2 diabetic or metabolic syndrome patients. The thiazolidinediones also potently lower circulating glucose levels of Type 2 diabetic animal models and humans. However, the fibrate class of compounds are without beneficial effects on glycaemia. Studies on the molecular actions of these compounds indicate that thiazolidinediones and fibrates exert their action by activating distinct transcription factors of the peroxisome proliferator activated receptor (PPAR) family, resulting in increased and decreased expression of specific enzymes and apolipoproteins respectively, both key-players in regulation of plasma triglyceride content. Fibrates, on the one hand, are PPAR α activators, acting primarily in the liver. Thiazolidinediones, on the other hand, are high affinity ligands for PPAR γ acting primarily on adipose tissue.

20

Adipose tissue plays a central role in lipid homeostasis and the maintenance of energy balance in vertebrates. Adipocytes store energy in the form of triglycerides during periods of nutritional affluence and release it in the form of free fatty acids at times of nutritional deprivation. The development of white adipose tissue is the result of a continuous differentiation process throughout life. Much evidence points to the central role of PPAR γ

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activation in initiating and regulating this cell differentiation. Several highly specialised proteins are induced during adipocyte differentiation, most of them being involved in lipid storage and metabolism. The exact link from activation of PPAR γ to changes in glucose metabolism, most notably a decrease in insulin resistance in muscle, has not yet been clarified. A possible link is via free fatty acids such that activation of PPAR γ induces Lipoprotein Lipase (LPL), Fatty Acid Transport Protein (FATP) and Acyl-CoA Synthetase (ACS) in adipose tissue but not in muscle tissue. This, in turn, reduces the concentration of free fatty acids in plasma dramatically, and due to substrate competition at the cellular level, skeletal muscle and other tissues with high metabolic rates eventually switch from fatty acid oxidation to glucose oxidation with decreased insulin resistance as a consequence.

PPAR α is involved in stimulating β -oxidation of fatty acids. In rodents, a PPAR α -mediated change in the expression of genes involved in fatty acid metabolism lies at the basis of the phenomenon of peroxisome proliferation, a pleiotropic cellular response, mainly limited to liver and kidney and which can lead to hepatocarcinogenesis in rodents. The phenomenon of peroxisome proliferation is not seen in man. In addition to its role in peroxisome proliferation in rodents, PPAR α is also involved in the control of HDL cholesterol levels in rodents and humans. This effect is, at least partially, based on a PPAR α -mediated transcriptional regulation of the major HDL apolipoproteins, apo A-I and apo A-II. The hypotriglyceridemic action of fibrates and fatty acids also involves PPAR α and can be summarised as follows: (I) an increased lipolysis and clearance of remnant particles, due to changes in lipoprotein lipase and apo C-III levels, (II) a stimulation of cellular fatty acid uptake and their subsequent conversion to acyl-CoA derivatives by the induction of fatty acid binding protein and acyl-CoA synthase, (III) an induction of fatty acid β -oxidation pathways, (IV) a reduction in fatty acid and triglyceride synthesis, and finally (V) a decrease in VLDL production. Hence, both enhanced catabolism of triglyceride-rich particles as well as reduced secretion of VLDL particles constitutes mechanisms that contribute to the hypolipidemic effect of fibrates.

A number of compounds have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia (U.S. Pat. 5,306,726, PCT Publications nos. WO91/19702, WO 95/03038, WO 96/04260, WO 94/13650, WO 94/01420, WO 97/36579, WO 97/25042, WO 95/17394, WO 99/08501, WO 99/19313 and WO 99/16758).

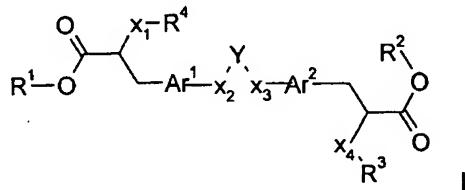
SUMMARY OF THE INVENTION

Glucose lowering as a single approach does not overcome the macrovascular complications associated with Type 2 diabetes and metabolic syndrome. Novel treatments of Type 2 diabetes and metabolic syndrome must therefore aim at lowering both the overt hypertriglyceridaemia associated with these syndromes as well as alleviation of hyperglycaemia.

The clinical activity of fibrates and thiazolidinediones indicates that research for compounds displaying combined PPAR α and PPAR γ activation should lead to the discovery of efficacious glucose and triglyceride lowering drugs that have great potential in the treatment of Type 2 diabetes and the metabolic syndrome (i.e. impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

15 DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to compounds of the general formula (I):



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wherein R¹, R², R³ and R⁴ independently of each other are hydrogen, C₁₋₁₂-alkyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or C₁₋₆-alkoxyC₁₋₆-alkyl, optionally substituted with one or more halogen, hydroxy or amino; and

25

X₁, X₂, X₃ and X₄ independently of each other is carbon, oxygen, sulphur or nitrogen; and

Y is C₁₋₁₂-alkyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, aralkyl, alkylaralkyl, heteroaryl, heteroaralkyl, or alkylheteroaralkyl, optionally substituted with one or more halogen, hydroxy or amino; and

30

Ar¹ and Ar² independently of each other are aryl or heteroaryl optionally substituted with one or more halogen, hydroxy, amino, aminoalkyl, carboxyalkyl, C₁₋₆-alkyl or C₁₋₆-alkoxy; or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

5

Preferred compounds of the invention are:

Ethyl 2-ethoxy-3-(4-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-but-2-enyloxy)-phenyl)-propionate,

10 2-Ethoxy-3-(4-(4-(2-ethoxy-2-hydroxycarbonyl-ethyl)-phenyloxy)-but-2-enyloxy)-phenyl)-propionic acid,

Ethyl 2-ethoxy-3-(4-(4-((4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-methyl)-benzyloxy)-phenyl)-propionate,

Ethyl 2-ethoxy-3-(4-(4-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-but-2-ynyloxy)-phenyl)-propionate,

15 2-Ethoxy-3-(4-(4-((4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-methyl)-benzyloxy)-phenyl)-propionic acid,

2-Ethoxy-3-(4-(4-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-but-2-ynyloxy)-phenyl)-propionic acid;

20

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

In the above structural formulas and throughout the present specification, the following terms 25 have the indicated meaning:

The term "C_{1-n}-alkyl" wherein n' can be from 2 through 12, as used herein, represents a branched or straight or cyclic alkyl group having from one to the specified number of carbon atoms. Examples of such groups include, but are not limited to methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and the like and cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like.

30 The terms "C_{2-n}-alkenyl" wherein n' can be from 3 through 12, as used herein, represents an olefinically unsaturated branched or straight group having from 2 to the specified number of carbon atoms and at least one double bond. Examples of such groups include, but are not 35

limited to, vinyl, 1-propenyl, 2-propenyl, allyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, hex-
enyl, pentenyl and the like.

5 The terms "C_{2-n}-alkynyl" wherein n' can be from 3 through 12, as used herein, represent an
unsaturated branched or straight group having from 2 to the specified number of carbon at-
oms and at least one triple bond. Examples of such groups include, but are not limited to, 1-
propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl and the like.

10 The term "C₁₋₆-alkoxy" as used herein, alone or in combination is intended to include those C₁₋₆-
alkyl groups of the designated length in either a linear or branched or cyclic configuration linked
through an ether oxygen having its free valence bond from the ether oxygen. Examples of linear
alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the like. Examples of
branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy, isohexoxy and the like.
15 Examples of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and
the like.

20 The term "C₁₋₆-alkoxyC₁₋₆-alkyl" as used herein, alone or in combination, refers to a C₁₋₆-alkyl
as defined herein whereto is attached a C₁₋₆-alkoxy as defined herein, e.g. methoxymethyl,
ethoxymethyl, methoxyethyl, ethoxyethyl and the like.

25 The term "aryl" is intended to include aromatic rings, such as carboxylic aromatic rings selected
from the group consisting of phenyl, naphthyl, (1-naphthyl or 2-naphthyl) and the like optionally
substituted with halogen, amino, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy and the like.

25 The term "halogen" means fluorine, chlorine, bromine or iodine.

30 The term "heteroaryl" as used herein, alone or in combination, refers to a monovalent
substituent comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered
bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen
and sulfur, e.g. furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine,
pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline,
isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and
purine and the like.

The term "arylalkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-(1-naphthyl)ethyl and the like.

- 5 The term "heteroarylalkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with a heteroaryl group; such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl and the like.
- 10 Certain of the above defined terms may occur more than once in the above formula (I), and upon such occurrence each term shall be defined independently of the other.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable base addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, sulphates, nitrates, phosphates, perchlorates, borates, acetates, benzoates, hydroxynaphthalates, glycerophosphates, ketoglutarates and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like. Examples of organic bases include lysine, arginine, guanidine, diethanolamine, choline and the like.

The pharmaceutically acceptable salts are prepared by reacting the compound of formula I with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hy-

dride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guandine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula I may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, amino acids, amino alcohols derived from amino acids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula I may be prepared by hydrolysing the pure diastereomeric amide.

Various polymorphs of compound of general formula I forming part of this invention may be prepared by crystallization of compound of formula I under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

Furthermore, the present compounds of formula I can be utilised in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

5 The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active pharmaceutical substances. In general, such prodrugs will be functional derivatives of the present compounds, which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives

10 15 are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

15 In a further aspect, the present invention relates to a method of treating and/or preventing Type I or Type II diabetes, preferably Type II diabetes.

20 In a still further aspect, the present invention relates to the use of one or more compounds of the general formula I or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment and/or prevention of Type I or Type II diabetes, preferably Type II diabetes.

In a still further aspect, the present compounds are useful for the treatment and/or prevention of IGT.

25 30 In a still further aspect, the present compounds are useful for the treatment and/or prevention of Type 2 diabetes.

In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from IGT to Type 2 diabetes.

30 In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

In another aspect, the present compounds reduce blood glucose and triglyceride levels and are accordingly useful for the treatment and/or prevention of ailments and disorders such as diabetes and/or obesity.

5 In still another aspect, the present compounds are useful for the treatment and/or prophylaxis of insulin resistance (Type 2 diabetes), impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, hyperglycaemia, atherosclerosis, hyperlipidemia, coronary artery disease, myocardial ischemia and other cardiovascular disorders.

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In still another aspect, the present compounds are effective in decreasing apoptosis in mammalian cells such as beta cells of Islets of Langerhans.

15 In still another aspect, the present compounds are useful for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis.

20 In still another aspect, the present compounds may also be useful for improving cognitive functions in dementia, treating diabetic complications, psoriasis, polycystic ovarian syndrome (PCOS) and prevention and treatment of bone loss, e.g. osteoporosis.

25 The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound of the formula I or any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers or diluents.

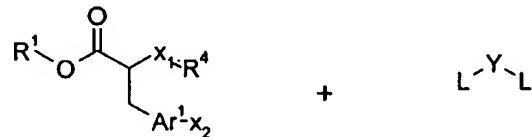
30 Furthermore, the invention relates to the use of compounds of the general formula I or their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof for the preparation of a pharmaceutical composition for the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR) such as the conditions mentioned above.

The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates.

5 A compound of formula I can be prepared as described below:

Reacting two molecules of a compound of formula II with one molecule of a compound of formula III, wherein R^1 , R^4 , Ar^1 , x_1 , x_2 and Y are as described above, with the exception that x_2 is not carbon and R^1 is not hydrogen, and L is a leaving group like halogen, mesyloxy or

10 hydroxy under Mitsunobo conditions



II

III

15

to give a compound of formula I with $R^1=R^2$ and $R^4=R^3$,

or by reacting one molecule of a compound of formula II with one molecule of a compound of formula III, followed by a reaction of the generated compound of formula IV with a compound of formula V, wherein R^1 , R^2 , R^3 , R^4 , Ar^1 , Ar^2 , x_1 , x_2 , x_3 , x_4 and Y are as described above, with the exception that x_2 and x_3 are not carbon and R^1 and R^2 are not hydrogen, and L is a leaving group like halogen, mesyloxy or hydroxy, under Mitsunobu conditions,



25

IV

V

to give a compound of formula I,

or hydrolyse the compound of formula I with R¹ and R² different from hydrogen, to give a

5 compound of formula I with R¹=R²= hydrogen.

PHARMACOLOGICAL METHODS

In vitro PPAR alpha and PPAR gamma activation activity.

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Principle

The PPAR gene transcription activation assays were based on transient transfection into human HEK293 cells of two plasmids encoding a chimeric test protein and a reporter protein 15 respectively. The chimeric test protein was a fusion of the DNA binding domain (DBD) from the yeast GAL4 transcription factor to the ligand binding domain (LBD) of the human PPAR proteins. The PPAR LBD harbored in addition to the ligand binding pocket also the native activation domain (activating function 2 = AF2) allowing the fusion protein to function as a PPAR ligand dependent transcription factor. The GAL4 DBD will force the fusion protein to bind only to Gal4 enhancers (of which none existed in HEK293 cells). The reporter plasmid 20 contained a Gal4 enhancer driving the expression of the firefly luciferase protein. After transfection, HEK293 cells expressed the GAL4-DBD-PPAR-LBD fusion protein. The fusion protein will in turn bind to the Gal4 enhancer controlling the luciferase expression, and do nothing in the absence of ligand. Upon addition to the cells of a PPAR ligand, luciferase protein 25 will be produced in amounts corresponding to the activation of the PPAR protein. The amount of luciferase protein is measured by light emission after addition of the appropriate substrate.

Methods

30

Cell culture and transfection: HEK293 cells were grown in DMEM + 10% FCS, 1% PS. Cells were seeded in 96-well plates the day before transfection to give a confluence of 80 % at transfection. 0,8 µg DNA per well was transfected using FuGene transfection reagent according to the manufacturers instructions (Boehringer-Mannheim). Cells were allowed to express protein for 48 h followed by addition of compound.

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Plasmids: Human PPAR α and γ was obtained by PCR amplification using cDNA templates from liver, intestine and adipose tissue respectively. Amplified cDNAs were cloned into pCR2.1 and sequenced. The LBD from each isoform PPAR was generated by PCR (PPAR α :

5 PPAR γ : aa 167 - C-term; PPAR γ : aa 165 - C-term) and fused to GAL4-DBD by subcloning fragments in frame into the vector pM1 generating the plasmids pM1 α LBD and pM1 γ LBD. Ensuing fusions were verified by sequencing. The reporter was constructed by inserting an oligonucleotide encoding five repeats of the Gal4 recognition sequence into the pGL2 vector (Promega).

10

Compounds: All compounds were dissolved in DMSO and diluted 1:1000 upon addition to the cells. Cells were treated with compound (1:1000 in 200 μ l growth medium including de-lipidated serum) for 24 h followed by luciferase assay.

15 Luciferase assay: Medium including test compound was aspirated and 100 μ l PBS incl. 1mM Mg $^{++}$ and Ca $^{++}$ was added to each well. The luciferase assay was performed using the Lu- cLite kit according to the manufacturers instructions (Packard Instruments). Light emission was quantified by counting SPC mode on a Packard Instruments top-counter.

20 PHARMACEUTICAL COMPOSITIONS

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the general formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or 25 diluent.

The present compounds may also be administered in combination with one or more further pharmacologically active substances eg. selected from antiobesity agents, antidiabetics, antihypertensive agents, agents for the treatment and/or prevention of complications resulting 30 from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity.

Thus, in a further aspect of the invention the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, uro-
5 cortin agonists, β 3 agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyrotropin releasing
10 hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, RXR (retinoid X receptor) modu-
lators or TR β agonists.

In one embodiment of the invention the antiobesity agent is leptin.
15 In another embodiment the antiobesity agent is dexamphetamine or amphetamine.
In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.
20 In still another embodiment the antiobesity agent is sibutramine.
In a further embodiment the antiobesity agent is orlistat.
In another embodiment the antiobesity agent is mazindol or phentermine.
25 Suitable antidiabetics comprise insulin, GLP-1 (glucagon like peptide-1) derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference as well as orally active hypoglycaemic agents.
30 The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists such as those disclosed in WO 99/01423 to Novo Nordisk A/S and Agouron Pharmaceuticals, Inc., GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or
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glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents as HMG CoA inhibitors (statins), compounds lowering food intake, RXR agonists and agents acting on the ATP-dependent potassium channel of the β -cells.

5

In one embodiment of the invention the present compounds are administered in combination with insulin.

10 In a further embodiment the present compounds are administered in combination with a sulphonylurea eg. tolbutamide, glibenclamide, glipizide or glicazide.

In another embodiment the present compounds are administered in combination with a biguanide eg. metformin.

15 In yet another embodiment the present compounds are administered in combination with a meglitinide eg. repaglinide.

In a further embodiment the present compounds are administered in combination with an α -glucosidase inhibitor eg. miglitol or acarbose.

20

In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β -cells eg. tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

25 Furthermore, the present compounds may be administered in combination with nateglinide.

In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg. cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

30

In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg. in combination with a sulphonylurea and metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin, insulin and lovastatin, etc.

35

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β -blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and

5 ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α -blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

10 It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more further pharmacologically active substances are considered to be within the scope of the present invention.

15 Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

20 Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used.

25 For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some

30 examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include

35

any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, 5 sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds. 10

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, in- 15 transal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin 20 capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier 25 may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil. 30

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in 35 cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:

5 Active compound (as free compound or salt thereof) 5 mg
Colloidal silicon dioxide (Aerosil) 1.5 mg
Cellulose, microcryst. (Avicel) 70 mg
Modified cellulose gum (Ac-Di-Sol) 7.5 mg
Magnesium stearate Ad.

10

Coating:

HPMC approx. 9 mg
*Mywacett 9-40 T approx. 0.9 mg

15 *Acylated monoglyceride used as plasticizer for film coating.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of diseases related to the regulation of blood sugar.

20 Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 25 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 0.1 mg to about 70 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a dosage of from about 2 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which 30 administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

35 Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.1 to about 100 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonary or transdermal administration comprise from about 0.001 mg to about 100 mg, preferably from about 0.01 mg to about 50 mg of the compounds of formula I admixed with a pharmaceutically acceptable carrier or diluent.

5

Any novel feature or combination of features described herein is considered essential to this invention.

EXAMPLES

10

The process for preparing compounds of formula I and preparations containing them is further illustrated in the following examples, which however, are not to be construed as limiting.

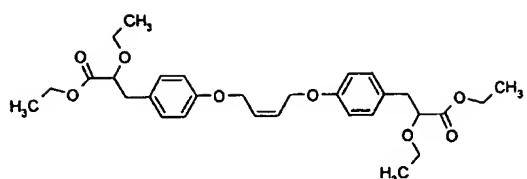
15 The structures of the compounds are confirmed by either elemental analysis (MA) nuclear magnetic resonance (NMR) or mass spectrometry (MS). NMR shifts (δ) are given in parts per million (ppm) and only selected peaks are given. mp is melting point and is given in $^{\circ}\text{C}$. Column chromatography was carried out using the technique described by W.C. Still et al, *J. Org. Chem.* 1978, 43, 2923-2925 on Merck silica gel 60 (Art 9385). Compounds used as starting materials are either known compounds or compounds which can readily be prepared 20 by methods known per se.

Abbreviations:

TLC:	thin layer chromatography
DMSO:	dimethylsulfoxide
25 CDCl ₃ :	deuteronated chloroform
DMF:	N,N-dimethylformamide
min:	minutes
h:	hours

30

Example 1

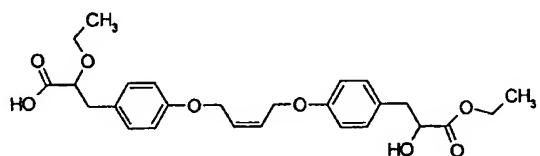


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Ethyl 2-ethoxy-3-(4-(4-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-but-2-enyloxy)-phenyl)-propionate.

10 To a solution of 2-buten-1,4-diol (0.5 mmol, 45mg) in THF (15 ml) was added triphenyl-phosphine (1.5 mmol, 393 mg). The reaction mixture was cooled to 0 °C and diethyl azodicarboxylate (1.5 mmol, 261 mg) was added drop wise, followed by addition of a solution of ethyl 3-(4-hydroxyphenyl)-2-ethoxy-propionic acid (2.0 mmol, 477mg) in THF (2 ml). The reaction was stirred at 0 °C for 2 hours and at room temperature for 8 days. Water was added
 15 and the mixture extracted with methylene chloride (2x25 ml). The combined organic phases were dried and evaporated to give the crude title compound. Purification on column chromatography using methylenechloride: ethyl acetate (5:1) gave the pure title compound in 109 mg (41%) yield. $^1\text{H-NMR}$ δ (CDCl_3) 7.15 (d, 4H), 6.84 (d, 4H), 5.92 (m, 2H), 4.65 (d, 4H), 4.17 (q, 4H), 3.97 (t, 2H), 3.67-3.55 (m, 2H), 3.42-3.30 (m, 2H), 2.95 (d, 4H), 1.23 (t, 6H), 1.15 (t, 20 6H).

Example 2



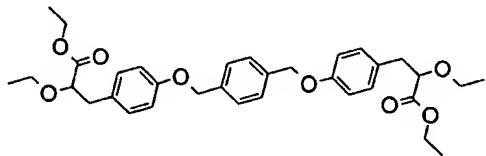
25

2-Ethoxy-3-(4-(4-(2-ethoxy-2-hydroxycarbonyl-ethyl)-phenyloxy)-but-2-enyloxy)-phenyl)-propionic acid.

Ethyl 2-ethoxy-3-(4-(4-(2-ethoxy-2-hydroxycarbonyl-ethyl)-phenyloxy)-but-2-enyloxy)-phenyl)-propionate (0.210 mmol, 109 mg) was dissolved in ethanol (7 ml) by heating to 60 °C. 1M NaOH (2.3 ml) was added and the reaction mixture was stirred at 90 °C for 90 min. The reaction mixture was evaporated and 1 N HCl (6.5 ml) and methylene chloride (30 ml) was added to the residue. The organic phase was collected and the aqueous phase was further extracted with methylene chloride (2x 25 ml). The combined organic phases were dried and evaporated to give the title compound in 87 mg (88 %) yield. $^1\text{H-NMR}$ δ (CDCl_3) 9.55 (br. s, 2H), 7.17 (d, 4H), 6.80 (d, 4H), 5.91 (m, 2H), 4.65 (d, 4H), 4.05 (m, 2H), 3.70-3.57 (m, 2H), 3.50-3.35 (m, 2H), 3.10-2.90 (m, 4H), 1.21 (t, 6H).

Example 3

15

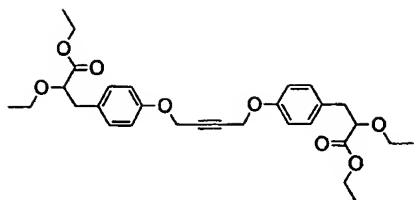


Ethyl 2-ethoxy-3-(4-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-methyl)-benzyloxy-phenyl)-propionate.

Was made as described under example 1, using 1,4-benzenedimethanol instead of 2-buten-1,4-diol. Yield 1.29 g (60 %). $^1\text{H-NMR}$ δ (CDCl_3) 7.45 (s, 4H), 7.15 (d, 4H), 6.85 (d, 4H), 5.04 (s, 4H), 4.16 (q, 4H), 3.97 (t, 2H), 3.70-3.51 (m, 2H), 3.45-3.27 (m, 2H), 3.95 (d, 4H), 1.4 (t, 6H), 1.15 (t, 6H).

25

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Example 4

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Ethyl 2-ethoxy-3-(4-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-but-2-nyloxy)-phenyl)-propionate.

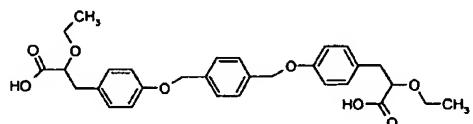
Was made as described under example 1, using 2-butyn-1,4-diol instead of 2-buten-1,4-diol.

Yield 171 mg (65%). $^1\text{H-NMR}$ δ (CDCl_3) 7.17 (d, 4H), 6.85 (d, 4H), 4.71 (s, 4H), 4.18 (q, 4H),

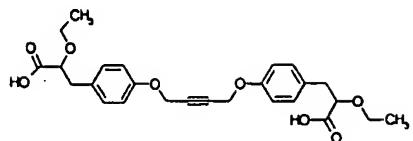
10 3.98 (t, 2H), 3.70-3.53 (m, 2H), 3.45-3.27 (m, 2H), 2.96 (d, 4H), 1.25 (t, 6H), 1.18 (t, 6H).

Example 5

15

**20 2-Ethoxy-3-(4-((4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-methyl)-benzyloxy)-phenyl)-propionic acid.**Was made as described under Example 2. Yield 135 mg (86%). $^1\text{H-NMR}$ δ (CDCl_3) 7.37 (s, 4H), 7.08 (d, 4H), 6.80 (d, 4H), 4.98 (s, 4H), 3.99 (m, 2H), 3.60-3.36 (m, 4H), 3.05-2.85 (m, 4H), 1.14 (t, 6H).

25

Example 6

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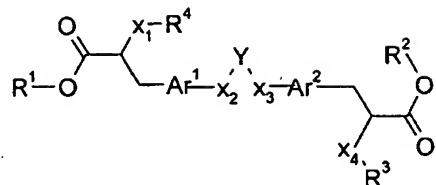
2-Ethoxy-3-(4-(4-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-but-2-ynyl)-phenyl)-propionic acid.

Was made as described under Example 2. Yield 150 mg (100%). $^1\text{H-NMR}$ δ (CDCl_3) 7.5 (br. s, 2H), 7.16 (d, 4H), 6.85 (d, 4H), 4.68 (s, 4H), 4.04 (m, 2H), 3.68-3.57 (m, 2H), 3.50-3.37 (m, 2H), 3.12-2.93 (m, 4H), 1.17 (t, 6H).

Claims:

1. A compound of formula (I)

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wherein R¹, R², R³ and R⁴ independently of each other are hydrogen, C₁₋₁₂-alkyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or C₁₋₆-alkoxyC₁₋₆-alkyl,
10 optionally substituted with one or more halogen, hydroxy or amino; and

x₁, x₂, x₃ and x₄ independently of each other is carbon, oxygen, sulphur or nitrogen; and

Y is C₁₋₁₂-alkyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, aralkyl, alkylaralkyl, heteroaryl, heteroaralkyl,
15 or alkylheteroaralkyl, optionally substituted with one or more halogen, hydroxy or amino; and

Ar¹ and Ar² independently of each other are aryl or heteroaryl optionally substituted with one or more halogen, hydroxy, amino, aminoalkyl, carboxyalkyl, C₁₋₆-alkyl or C₁₋₆-alkoxy;

20 or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

2. The compound according to claim 1 which is

25 Ethyl 2-ethoxy-3-(4-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-but-2-enyloxy)-phenyl)-propionate,
2-Ethoxy-3-(4-(4-(2-ethoxy-2-hydroxycarbonyl-ethyl)-phenyloxy)-but-2-enyloxy)-phenyl)-propionic acid,
Ethyl 2-ethoxy-3-(4-(4-((4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-methyl)-benzyloxy)-phenyl)-propionate,
30 Ethyl 2-ethoxy-3-(4-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-but-2-nyloxy)-phenyl)-propionate,

2-Ethoxy-3-(4-(4-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-methyl)-benzyloxy)-phenyl)-propionic acid,

2-Ethoxy-3-(4-(4-(2-ethoxy-2-ethoxycarbonyl-ethyl)-phenyloxy)-but-2-ynyl)-phenyl)-propionic acid;

5

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

10 3. A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

15 4. A composition according to claim 3 in unit dosage form, comprising from about 0.05 to about 100 mg, preferably from about 0.1 to about 50 mg of the compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof.

20 5. A pharmaceutical composition useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

25 6. A pharmaceutical composition useful in the treatment and/or prevention of diabetes and/or obesity, the composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

7. A pharmaceutical composition according to any one of the claims 3-6 for oral, nasal, transdermal, pulmonary, or parenteral administration.

30

8. A method for the treatment of ailments, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding claims 3-7.

35

9. A method for the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding claims 3-7.
 - 5
10. A method for the treatment and/or prevention of diabetes and/or obesity, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding claims 3-7.
 - 10
11. The method according to claims 8, 9 or 10, wherein the effective amount of the compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt or ester thereof is in the range of from about 0.05 to about 100 mg per day, preferably from about 0.1 to about 50 mg per day.
 - 15
12. Use of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament.
 - 20
13. Use of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).
 - 25
14. Use of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment and/or prevention of diabetes and/or obesity.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00236

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 69/612, A61K 31/215

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0597102 A1 (YAMANOUCHI PHARMACEUTICAL CO. LTD), 18 May 1994 (18.05.94), Compound VII --	1,3-7,12-14
A	Chemical Abstracts, Volume 65, No 3, 1 August 1966 (01.08.66), (Columbus, Ohio, USA), Elzbieta Wyrzykiewicz et al, "Optically active stilbene derivatives", page 1, THE ABSTRACT No 3781c-f, Zeszyty Nauk. Uniw. Poznaniu, Mat., Fiz., 1965, 9 (58), 29-45 -----	1,3-7,12-14

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 2001	19 -06- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Göran Karlsson/BS Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT1 ational application No.
PCT/DK01/00236**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **8-11**
because they relate to subject matter not required to be searched by this Authority, namely:
**A Method for treatment of the human or animal body by therapy,
Rule 39.1**
2. Claims Nos.: **1, 3-7, 12-14**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK01/00236

Box 1,2

The present claims 1, 3-7 and 12-14 relate to an extremely large number of possible compounds. Further, the definition of the divalent groups in formula I x1, x2, x3 and x4 is not clear because the groups "carbon", "sulphur" and "nitrogen" have or can have more than two substituents.

Due to these deficiencies, the search has been limited to the compounds considered to be more relevant. Only the meaning "oxygen" for x1, x2, x3 and x4 have been searched.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/05/01

International application No.	
PCT/DK 01/00236	

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0597102 A1	18/05/94	SE 0597102 T3	
		AU 663514 B	12/10/95
		DE 69228122 D, T	24/06/99
		DK 597102 T	09/08/99
		FI 940419 A	28/01/94
		KR 204938 B	15/06/99
		NO 940312 A	17/03/94
		US 5508296 A	16/04/96
		AT 175409 T	15/01/99
		AU 2346592 A	02/03/93
		CA 2114001 A	18/02/93
		ES 2128355 T	16/05/99
		HU 70421 A	30/10/95
		HU 9400244 D	00/00/00
		WO 9303021 A	18/02/93